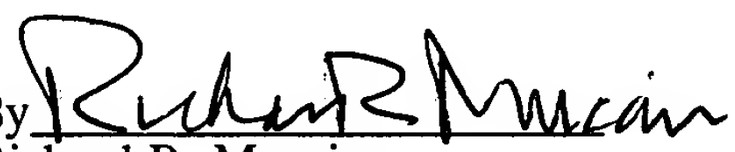
art to expect the process used to produce the claimed product would fail does not establish obviousness. *In re Dow Chem. Co.* (CAFC 1988) 5 U.S.P.Q.2d 1529.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. It is not proper within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggest to one of ordinary skill in the art. The references of record fail to teach or suggest applicants' invention as a whole.

Applicants request the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments which might be most expeditiously handled by a telephone conference. Applicants' attorney authorizes the Examiner to charge Deposit Account 13-4822 if there are any additional charges in connection with this Response.

Respectfully submitted,
Stanley E. Katz and Alain Martin

By 
Richard R. Muccino
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Display Abstract Show: 20 Sort Send to Text

1: Ann Allergy. 1988 Oct;61(4):305-10.

Related Articles, Lir

Comparative tolerability of two formulations of Rhinalar (flunisolide) nasal spray in patients with seasonal allergic rhiniti

Greenbaum J, Leznoff A, Schulz J, Mazza J, Tobe A, Miller D.

Syntex Inc, Mississauga, Ontario, Canada.

This double-blind, randomized, crossover study compared the incidence of nasal burning and stinging, as well as overall tolerability of the currently marketed formulation of Rhinalar (original formulation) to a new formulatio of Rhinalar containing less propylene glycol. In addition, patient and investigator subjective evaluations were used to compare the effectiveness of the test medications in controlling the nasal symptoms of seasonal allergic rhinitis. A total of 122 patients were enrolled in this 4-week trial. Each patier received one formulation of Rhinalar for 2 weeks and then crossed over to receive the alternate formulation for an additional 2 weeks. Eighteen patients withdrew from the trial prematurely. Ten patients were lost to follow-up and eight withdrew due to side effects and/or inadequate therapeutic response. Statistical comparisons of patient evaluations of nasal burning and stinging with the two formulations of Rhinalar showed a very significant difference ir terms of severity (P less than .001), duration (P less than .001), and tolerabili (P = .006) in favour of the new formulation. A reduction in severity of throat irritation with the new formulation was also shown to be statistically significant (P = .006). Nausea, headache, and other side effects including watery eyes, taste perversion, and runny nose were seldom reported with either test medication. Both formulations were shown to be equally effective in relieving the nasal symptoms of seasonal allergic rhinitis. The considerabl reduction in nasal burning and stinging and throat irritation with the new formulation of Rhinalar was shown to enhance patient acceptability and may lead to better compliance.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 3052188 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

1: Food Chem Toxicol. 1989 Sep;27(9):573-83. Related Articles, Lir

Subchronic nose-only inhalation study of propylene glycol in Sprague-Dawley rats.

Suber RL, Deskin R, Nikiforov I, Fouillet X, Coggins CR.

Bowman Gray Technical Center, R. J. Reynolds Tobacco Co., Winston-Salem, NC 27102.

Groups of nineteen Sprague-Dawley rats of each sex were exposed by a nose only inhalation to 0.0, 0.16, 1.0 or 2.2 mg propylene glycol/litre air, for 6 hr/day, 5 days/wk for 90 days. There were no significant differences in respiratory rates, minute volumes or tidal volumes between any of the groups during aerosol exposure. The uniformity of respiratory parameters between dose groups implied that the delivered doses were proportional to the exposu concentrations. The mean terminal body weights were not significantly different from controls for any group of male animals. The mean body weigh of the females exposed to 2.2 mg/litre were significantly less than those of female controls from day 50 onwards. This effect, in female rats, was consistent with a decrease in feed consumption for the high-exposure female rats beginning on study day 43. Statistically significant differences between the treated and control groups in certain haematological parameters, serum enzyme activities, other serum chemistry parameters and organ weights did not show clear dose relationships. There was a significant increase in the number of goblet cells or an increase in the mucin content of the existing goblet cells in the nasal passages of the medium- and high-exposure animals. Exposure to the above concentrations of propylene glycol caused nasal haemorrhage and ocular discharge in a high proportion of animals, possibly a a result of dehydration of the nares and eyes.

PMID: 2807102 [PubMed - indexed for MEDLINE]

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1: Res Exp Med (Berl). 1989;189(1):39-42.

Related Articles, Lir

Effects of propylene glycol on redox state of the perfused rat liver--a note of caution.

Scholmerich J, Kitamura S, Miyai K.

Dept. of Pathology, University of California, San Diego, La Jolla.

Propylene glycol is used as a solvent for bile salts in studies on their biologic effects on the liver. While using this solvent (32-64 mmol/l) in the isolated perfused rat liver, we found a significant change in the extramitochondrial redox system as indicated by a fivefold increase of the lactate pyruvate ratio the perfusate. The increase was due to an increased uptake of pyruvate (0.8 mumol/g/min) and to a release of lactate (1.8 mumol/g/min). The intramitochondrial redox state was affected to a lesser degree as estimated by the beta-hydroxybutyrate acetoacetate ratio (twofold increase). These abnormalities resemble those induced by similar concentrations of ethanol. W suggest, therefore, that investigators studying bile acids should be aware of this artifact which causes significant alterations in cellular energy systems an enzyme activities.

PMID: 2711035 [PubMed - indexed for MEDLINE]

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1: Crit Rev Toxicol. 1999 Jul;29(4):331-65.

A review of the comparative mammalian toxicity of ethylene glycol and propylene glycol.

LaKind JS, McKenna EA, Hubner RP, Tardiff RG.

LaKind Associates, LLC, Catonsville, MD, USA.

The purpose of this article is to review and interpret the scientific literature o the mammalian toxicity of ethylene glycol (EG) and propylene glycol (PG), with the goal of comparing the toxicity of the two chemicals. This type of review may serve as the basis for risk management decision-making. Becaus EG is not a GRAS (generally recognized as safe) chemical, its uses are restricted when compared with PG; thus, certain routes of exposure are not relevant here for toxicological comparison (e.g., subcutaneous, intramuscula and intravenous). Therefore, this review is focused on the oral, inhalation, an dermal routes of exposure. However, where toxicological data derived from a alternative route of exposure serve to eludicate mechanisms of toxicity, data from these routes are considered. Based on the review provided herein, the following conclusions can be drawn. From the standpoint of lethality, acute effects, and reproductive, developmental, and kidney toxicity, the toxicity of EG exceeds that of PG. Further, localized dermal effects from EG and PG ar both mild, with data suggesting that PG may have a skin contact sensitizatior potential. Finally, PG exposure in laboratory animals has been associated wit reversible hematological changes; no data were located for EG from which t draw a toxicological comparison.

Publication Types:

- Review
- Review, Academic

PMID: 10451263 [PubMed - indexed for MEDLINE]

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1: J Am Vet Med Assoc. 1990 Jun 1;196(11):1816-9.

Effects of propylene glycol-containing diets on acetaminophen-induced methemoglobinemia in cats.

Weiss DJ, McClay CB, Christopher MM, Murphy M, Perman V.

Department of Veterinary Pathobiology, College of Veterinary Medicine, University of Minnesota, St Paul 55108.

Soft-moist cat foods contain 7 to 13% propylene glycol (PG) on a dry-weigh basis. These diets induce Heinz body formation in feline RBC. In this study, we evaluated cats on a control diet and on a commercial diet containing 8.3% PG. All cats on the PG diet developed an increase in the number of circulatin Heinz bodies. We then administered acetaminophen to cats on each diet to determine whether RBC from cats on PG diets were more susceptible to oxidant stress. Methemoglobin concentrations were significantly greater in cats in PG diets after acetaminophen administration. These data indicate that RBC from cats fed PG diets are more susceptible to oxidative stress.

PMID: 2351602 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

1: Pharmacotherapy. 1996 Jul-Aug;16(4):690-3.

Related Articles, Lir

Propylene glycol: the safe diluent that continues to cause harm.

Glover ML, Reed MD.

Division of Pediatric Pharmacology and Critical Care, Rainbow Babies and Childrens Hospital, Cleveland, OH 44106-6010, USA.

Propylene glycol (PG) is present in many pharmaceutical products, lotions, ointments, and cosmetics. Although considered to be a relatively safe substance, overdoses have been associated with serious adverse effects. Propylene glycol intoxication occurred in a child and caused central nervous system depression and a severe metabolic acidosis. Initial assessment reveale an elevated serum anion gap, a slight increase in measured serum osmolality, and a normal osmolal gap. The child's acidosis was due to increased concentrations of lactate and pyruvate. The possibility of serious PG intoxication should be considered in any patient with an unexplained serious metabolic acidosis.

Publication Types:
- Case Reports

PMID: 8840379 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

1: Biochem Med Metab Biol. 1989 Oct;42(2):87-94. Related Articles, Lir

Kinetics of oral propylene glycol-induced acute hyperlactatemia

Morshed KM, Nagpaul JP, Majumdar S, Amma MK.

Department of Biochemistry, Panjab University, Chandigarh, India.

The kinetics of PD-induced HL in rat have been investigated. The data obtained indicated that PD was solely responsible for the elevation (1.83- to 4.01-fold) of blood lactate that was sustained long enough to affect considerably the normal physiological function of the system. The productio of lactate increased as the dose of PD increased up to 38.66 mmole/kg, therel obeying the Michaelis-Menten kinetics model that gave an apparent Km and Vmax as 7.14 mmole/kg and 7.50 mmole/liter/hr, respectively. The t1/2 elimination time ranged from 1.40 to 5.82 hr which followed apparent first-order kinetics. Pyrazole inhibited (Ki = 6 mumole/kg) the PD-induced HL competitively, suggesting that alcohol dehydrogenase might have played a regulatory role in the conversion of PD to lactate. The PD-induced HL in rat and the LA in human patients are two distinct biochemical entities; reasoning has been given to substantiate that HL is lower order LA. Evidence has been presented to show that PD is a suitable and effective potential agent for producing experimental HL in rat in preference to agents that are currently being used.

PMID: 2789852 [PubMed - indexed for MEDLINE]

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